SYNOPSIS

"APPLICATIONS OF MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS WITH THEIR PHARMACOLOGICAL APPLICATIONS"

Short Resume Of The Plan Proposed For Investigation For Ph. D.

Degree Under The Faculty Of Science.

To be submitted to

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ABSTRACT

"APPLICATIONS OF MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS WITH THEIR PHARMACOLOGICAL APPLICATIONS"

1. Introduction:

Multicomponent reactions (MCRs) emerged as a powerful strategy in modern synthetic organic chemistry and constitute efficient alternatives to the step by step assembly of complex heterocyclic structures of importance for pharmaceutical development.On the other hand, the development of environmentally friendly heterogeneous reagents, known for long time for their low costs and toxicity, has received much attention since higher selectivities are usually observed and the products can be easilyisolated with good chemical purity by simple filtration avoiding time consuming and tedious extractive work-up.

Heterocyclic compounds shows various medicinal applications and broad occurrence in nature, particularly in biological systems like nucleic acids, heamoglobin, marine alkaloids, plant, hormones and enzymes. Organic synthesis is one of the special branch in chemical synthesis and is concerned with the construction of organic compounds by reactions. It is believed to be one of the most vital roles in organic chemistry because of the organic molecules used to contain higher level of complexity compared to pure inorganic compounds. So far, organic synthesis plays a very important role in many sectors such as pharmaceuticals, agricultural etc.Imidazo[1,2-*a*]pyridine[1], imidazo[1,2-*a*] pyrimidine[2] and imidazo[1,2-*a*]pyrazine[3] and benzo[*d*] imidazo [2,1-*b*] thiazoles, are important structural moieties found in numerous natural and synthetic bioactive molecules, and have received significant attention from the pharmaceutical industry owing together interesting biological activities displayed over abroad range of therapeutic classes. The members of these ring systems have several valuable biological properties and are used as hypotensive, antiulcer, oranxiolytic agents in addition to bradycardic,[4] antiasthmatic,[5] antimicrobial,[6] cytoprotective,[7] calcium channel blocking agents[8] and as HIF-1 α-prolylhydroxylase inhibitors.[9] Imidazo[1,2- *a*]pyridines are also an important pharmocophore in a number of drug

formulations currently available in the market.[10]Apart from the above, imidazo[1,2-*a*] pyridinium salts are also used to prepare styryl dyes.[11]

Multicomponent reactions (MCRs) are those reactions in which three or more reactants come together in a single reaction vessel to form a new product which contains the majority of the atoms of the starting materials."Upto seven component reactions have been described so far. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product.

The MCR satisfies many of the principals of Green Chemistry as reaction in solvent free conditions, starting material easily available, water as a solvent and atom economy. MCRs have several advantages over conventional organic reactions.

- **Simple One pot synthesis:** Even though diversity is a goal, one expects to form only a single product from a given set of inputs.
- **Atom economomical reactions:** The valuable property of MCRs in which adducts are composed of the exact sum of the reactants.
- **High yield:** MCRs are highly convergent as it tends to maximize the overall yield by minimizing the number of consecutive steps for each building block synthesis.

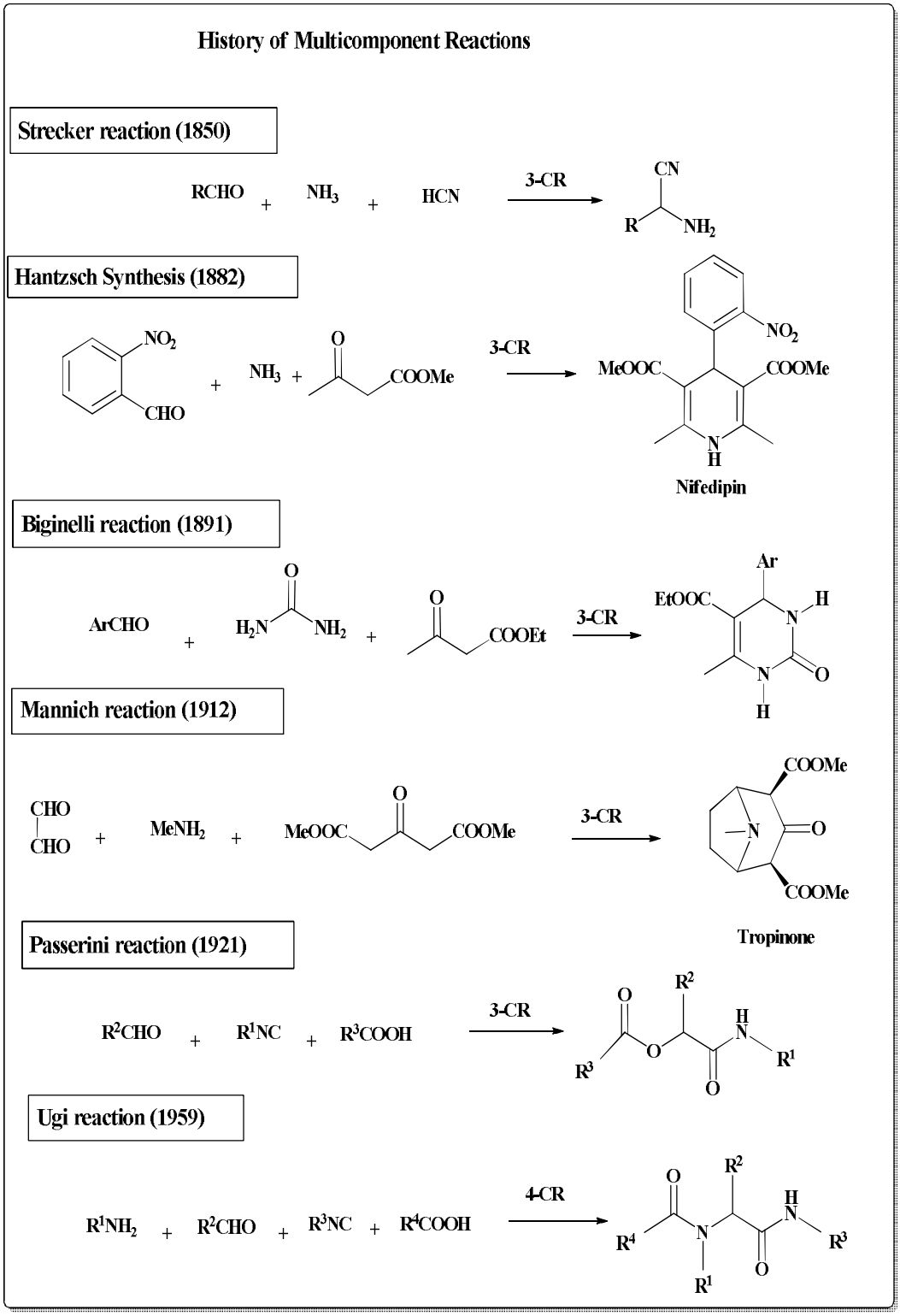
2. Review of literature and Development in the subject

(Previous work done in the relevant area):

Multicomponent reactions (MCRs) emerged as a powerful strategy in modern synthetic organic chemistry and constitute efficient alternatives to the step by step assembly of complex heterocyclic structures of importance for pharmaceutical development.On the other hand, the development of environmentally friendly heterogeneous reagents, known for long time for their low costs and toxicity, has received much attention since higher selectivity's are usually observed and the products can be easily isolated with good chemical purity by simple filtration avoiding time consuming and tedious extractive work-up.

Recently, scientific efforts focus more and more on the development of multi-component procedures for the generation of libraries of Heterocyclic Compounds. This growing interest is stimulated by the interesting pharmaceutical properties that are

associated with many heterocycles and their Structure Activity Relationship (SAR) studies.



3. Objectives of Research/ Proposed work:

1. To Design various heterocyclic compounds using MCR techniques with the help of various novel ecofriendly catalysts.
2. To study the pharmacological applications of these prepapred heterocyclic compounds.
3. Principals of Green chemistry as a new tool for the Improvement of these reactions.
4. MCR as a Key Step for the Construction of Core- framework of the Bio-active compounds as green synthesis i.e. the reagents, solvent are environmental friendly.

Multicomponant compounds have played important roles in the drug discovery process and in the isolation and structural identification of biological macromolecules. So an attempt will be made to synthesize such valuable heterocycles using MCR strategy.

Now a day's Green Chemistry has become a important tool in the field of, with the increasing environmental concerns and the regulatory constraints faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research. Therefore more and more chemist's synthetic endeavors are devoted toward 'green synthesis' which means the reagent, solvent and catalyst are environmentally friendly.

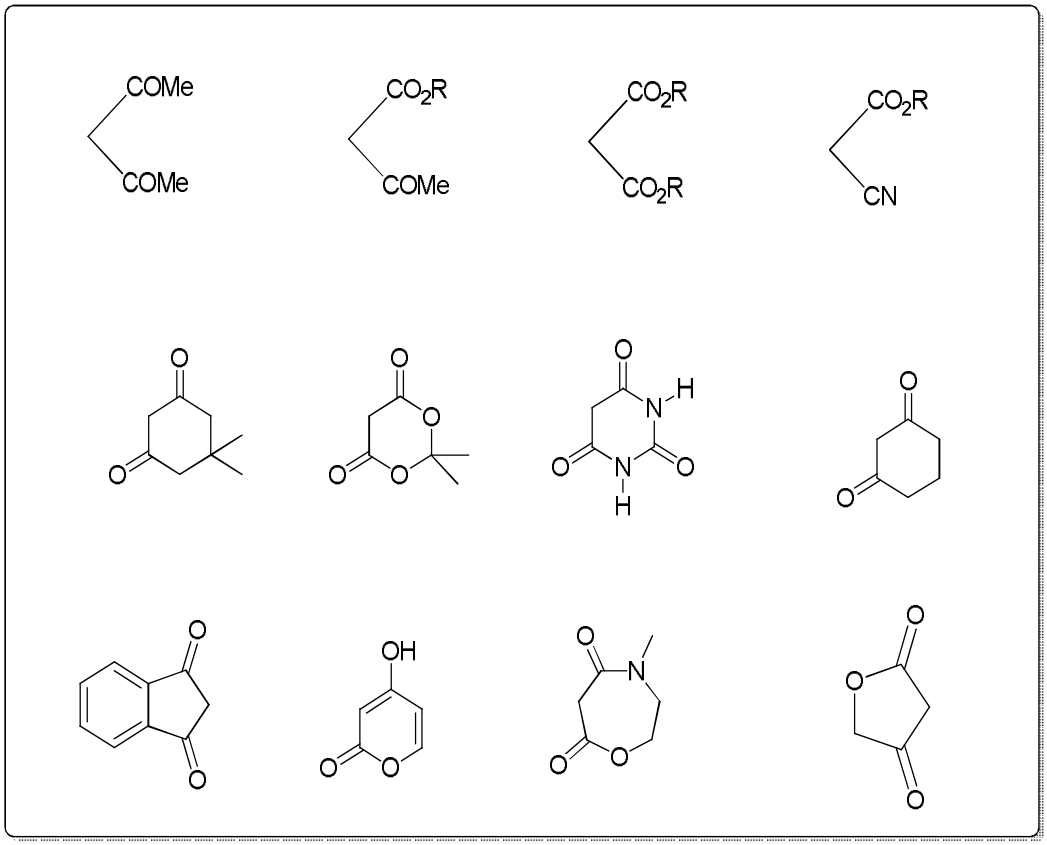
Bio-active natural products can be regarded as chemical entities that have been evolutionarily selected and validated for binding to particular protein domains. The synthesis of bio-active natural products will be one of the target of investigation with MCR as a key step.

4. Methodology to be adopted:

a) Utilization of 1,3–dicarbonyl compounds in MCRs

Utilisation of 1,3–dicarbonyls has not been the center of much interest and apart from the well known Hantzsch (1882), Biginelli and Robinson–Schopf reactions and more recently Tietze synthesis of dihydropyrans no other application has been reported to date. The aim of this research project is to utilize 1,3–dicarbonyl derivatives for the construction of highly functionalised small organic molecules of high synthetic and

biological value. The various cyclic and acyclic 1,3–dicarbonyl substrates commonly utilised in MCR are listed as follows

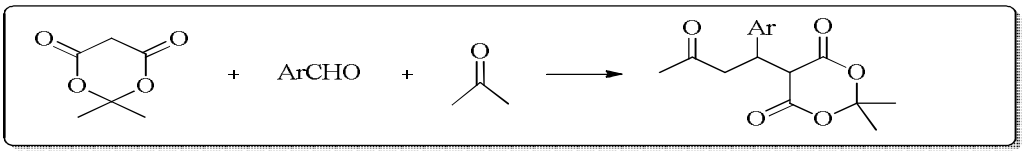


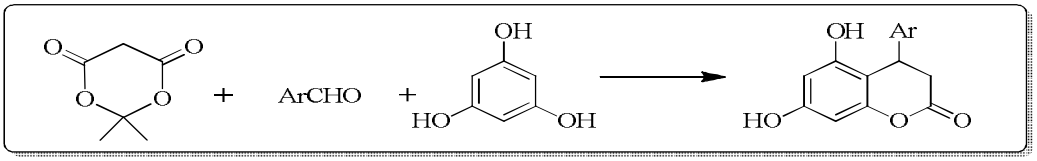
Although the reaction can be performed with a large variety of compounds possessing activated methylene groups, those bearing two electron-withdrawing substituents are usually employed. Among them, cyclic and acyclic 1,3-dicarbonyl derivatives are particularly common substrates.Thus, not only substances such as malonates, acetoacetates and acetylacetone, but also cyclic compounds such as 1,3-cyclohexanediones, Meldrum's acid, Barbituric acids, oxazepanediones and 4-hydroxycoumarins are frequently employed. The success of MCRs involving 1,3–dicarbonyl substrates is largely due to the Knoevenagel reaction. The mild reaction conditions, experimental simplicity and the low cost of the substrates has made Knoevenagel condensation worthy of high synthetic potential with a broad scope. Moreover, Knoevenagel products are highly reactive compounds because of their low energy LUMOs, so this sequence has been used in one-pot combination with other classical synthetic reactions, resulting in some very efficient multi-component

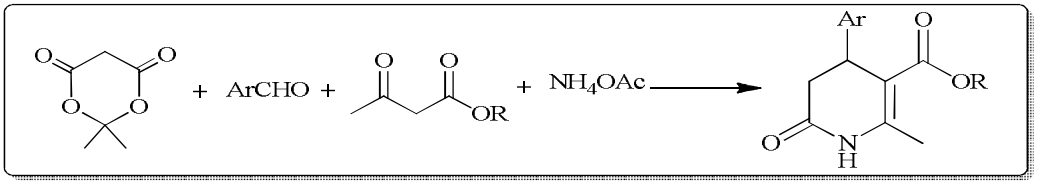
sequences. Among them Knovenagel-Michael and Knovenagel/ hetero Diels-Alder reactions are probably the most documented sequences.

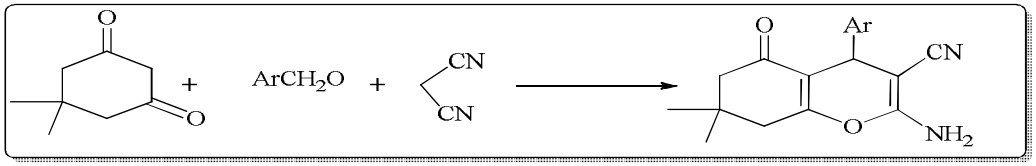
Future Plans: Based upon these NAME REACTIONS, following MCRs will be investigated:

Combination of Knoevenagel reaction with Michael Addition

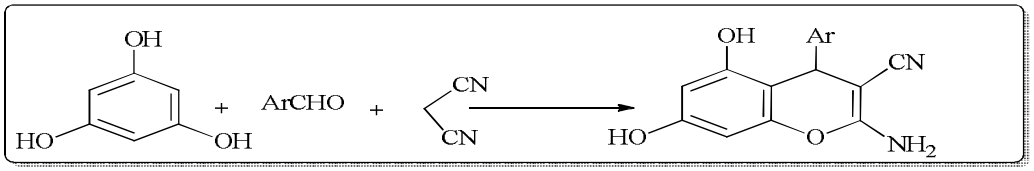




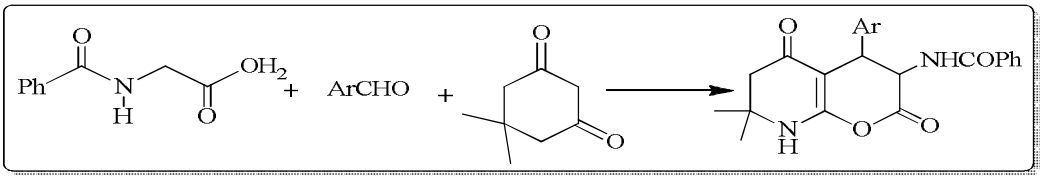


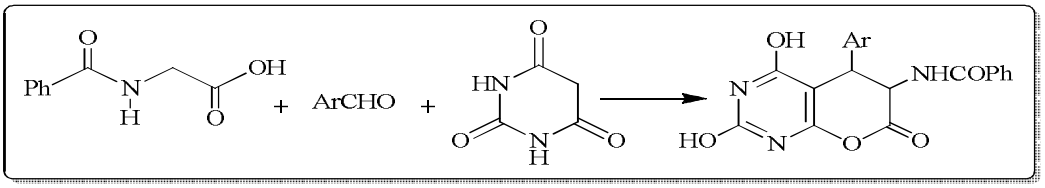


Knoevenagel Condensation and Friedel Crafts Reaction



Hippuric acid as a building block for the synthesis of MCR





5. Importance of study/ Society applications:

International Status :The first MCR, reported in 1850 by Strecker, this wellknown concept, also widely represented in nature, has been extensively used in both liquid-phase and solid-phase chemistry for the rapid assembly of complex heterocyclic structures of importance for pharmaceutical development. Although isocyanide-based MCRs, introduced in1921 by Passerini, generally predominate nowadays for the construction of widely diverse heterocycles,one of the first substrate classes involved in a MCR was that of 1,3-dicarbonyl derivatives, with Hantzsch's dihydro pyridine synthesis appearing as early as 1882. There are several groups working throughout the world on isocyanide based MCRs (i.e. IMCRs). Amongst all known MCRs, the group of Ugi-reactions (Prof. I. Ugi, Munchen-Germany) are by far the most versatile. More than two-dozen molecular scaffolds have been described so far. Using these MCRs, often by reacting archetypal starting materials such as carbonic acids, amines, ketones or aldehydes and isocyanides, very large numbers of analogues are accessible.

National Status: Dr. Vijay Nair, RRL, Trivandrum has effectively contributed to the field of Multi Componant Reactions. The work of Dr. Nair research group is focused on MCRs for the synthesis of several interesting heterocyclic structures.

Significance of the study: Although not a very new problem, both economic and ecological pressures, coupled with the concomitant emergence of high-throughput screening, are playing increasingly significant roles in the development of modern synthetic Organic Chemistry. Selectivity, atom economy, time saving, environmental friendliness, cost effectiveness and there conciliation of molecular complexity with experimental simplicity are some of the pieces of the puzzle needing to be assembled by modern academic and industrial synthetic chemists to reach the maximum of efficiency. All these constraints have resulted in tremendous development of new concepts and new methodologies able to produce valuable laborated compounds. In this context, utilization of multi component reactions (MCRs) involving domino processes, with at least three different simple substrates reacting in a well defined manner to form a single compound, has emerged as a powerful strategy. This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and is particularly well adapted for combinatorial chemistry.

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6.Proposedwork plan/ Formulation and structure of study:

- **Year-wise plan of work and targets to be achieve:**
- First 12 months are utilised for literature survey and the detail study the synthesis of compounds in MCRs.
- Next 12 months involves design of novel MCRs through combination various name reactions.
- In last 12 months all MCR compounds will be evaluated for their biological activity.
- Final draft of Ph. D. work.

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